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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,648	03/07/2001	Neil A. Williams	7438	3732

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	14

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,648	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-49* is/are pending in the application.

4a) Of the above claim(s) *29-33 and 36-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 March 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's response to the Restriction requirement filed on May 13, 2002 is acknowledged. Applicant's election of Group II with traverse, claims 34-38, species SEQ ID NO:2 is acknowledged. Claims 29-33, 39-44 and 45-49 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being to a non-elected invention. Claims 36-38 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being to a non-elected species. The traversal is on the grounds that Groups I-IV are believed to be so linked as to form a single general inventive concept. These arguments have been fully considered but are not found to be persuasive for the reasons below:

Groups I and III in this application and lack novelty, therefore the other claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept.

Restriction is required under 35 U.S.C. 121 and 372.

The MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example as product and method of use, etc., but are capable of separate manufacture, use or sale as claimed, and are patentable over each other (see MPEP 802.01). In the instant situation, Groups I-IV are drawn to different methods that require

different reagents, parameters and endpoints. Lack of unity exists when there is no shared "special technical feature" among the claimed inventions. A special technical feature is defined as a contribution which each of the inventions, considered as a whole, makes over the prior art. Groups I and II lack novelty under PCT Article 33(2) as being anticipated by Williams et al, *(U.S. Patent No. 6,287,563, filed December 29, 1997).* Williams et al discloses agents in the treatment or prevention of human cell leukemia, transplant rejection or graft-verses –host disease in a vaccination method for vaccinating a mammalian subject. Williams et al also disclose that the agents used in vaccinating a mammalian subject can be an agent having an effect on GM-1 binding mediated intracellular signaling events but no GM-1 binding activity (see the Abstract). Therefore, Group I is the main invention in this application and it lacks novelty, therefore the other claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept. It should be remembered that each Election/Restriction is an individual action. All requirements set forth in each Election/Restriction should stand alone and are not based on previous restriction requirements. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Specification Objections

2. The specification is objected because of what appears to be typographical errors. For example, page 6, line 6 the term "susbstance" should be changed to "substance". The applicant is asked to review the entire specification for spelling errors and correction is required.

3. The specification is objected because it discloses the genus and species of organisms and the genus and species of any organism should be underlined or italicized. See for example, page 36. Correction is required.

Drawings

4. The drawings are objected to by the Draftsman under 37 CFR 1.84 or 1.152. See the attached form PTO 948.

Priority

5. The priority date granted to the instant application is September 7, 1999 because the United Kingdom priority document 9819484.8 had not been received.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 34 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification discloses SEQ ID NO: 2, which corresponds to the amino acid sequence that is used in a method of treating a subject having an autoimmune disease, human T cell leukemia, transplant rejection or graft-versus host disease, allergies or infectious disease. The claims are directed to sequences that are at least 75% homologous to SEQ ID NO: 2 and corresponding sequences that are mixtures, homologues, variants and derivatives that have a variant degree of identity (similarity, homology), and so forth. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO: 2, 3,4 and 5 the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptide regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a

potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO: 2, 3, 4 and 5 but not the full breadth of the claim (or none of the sequences encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

7. Claims 34-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2, does not reasonably provide enablement for variants, homologs, derivatives or fragments of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a method of treating a subject having an autoimmune disease, human T cell leukemia, transplant rejection or graft-versus host disease, allergies or infectious disease comprising administering to the subject an effective amount of a peptide selected from the group consisting of SEQ ID NO 2, mixtures

thereof, homologues, variants, and derivatives of any of these, which exhibit activity the same or similar to EtxB or CtxB, but wherein the peptide does not exhibit GM-1 binding activity. The specification is enabling only for the peptide of SEQ ID NO: 2 and not mixtures, homologs, variants or derivatives of SEQ ID No:2 as disclosed in the specification. The specification discloses amino acid sequences according to the claimed invention that have at least 75% identity with the peptide of SEQ ID No:2" (page 16). The specification states that "% homology may be calculated over contiguous sequences, i.e. one sequence is aligned with the other sequence and each amino acid in the other sequence is directly compared with the corresponding amino acid in the other sequence, one residue at a time" (page 17). The specification states that "the terms variant or derivative in relation to the amino acid sequences of the present invention includes any substitution of, variation of, modification of, replacement of, deletion of or addition of one or more amino acids from or to the sequence providing the resultant entity retains an activity, preferably having at least the same and/or similar activity as CtxB and/or ExtB" (page 18). There is no guidance provided as to which nucleic acids can be added, deleted or substituted and still have the peptide retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of peptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the peptide determines its structural and functional properties, predictability of which changes can be tolerated in a peptide's amino acid sequence and still retain similar activity requires a

knowledge with regard to which amino acids in the peptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the peptide's structure relates to function. However, the problem of the prediction of peptide's structure from mere sequence data of a single peptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the peptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the peptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any peptide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some peptide is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such peptide.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other peptides having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use peptides that are variants, homologs, mixtures, derivatives or fragments of SEQ ID NO: 2 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the peptide's structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

8. Claims 34-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of treating a subject having an autoimmune disease, human T cell leukemia, transplant rejection or graft-versus host disease, allergies or infectious disease comprising administering to the subject an effective amount of a peptide selected from the groups consisting of SEQ ID NO:2, mixtures thereof, homologues, variants and derivatives of any of the these which exhibit activity the same or similar to enterotoxin B subunit (ExtB) or cholera toxin (CtxB) wherein the peptide does not exhibit GM-1 binding activity.

The specification has not enabled a method of treating a subject having an autoimmune disease, human T cell leukemia, transplant rejection or graft-verses host disease, allergies or infectious disease comprising administering to the subject an effective amount of a peptide wherein the peptide does not exhibit GM-1 binding activity. The specification has not made a correlation between EtxB or CtxB and autoimmune disease, human T cell leukemia, transplant rejection or graft-verses host disease, allergies or infectious disease. Nashar et al, *(Proc. Natl. Acad. Sci, USA, Vol.*

93. p. 226-230) teach that studies on the *in vitro* effects of cholera toxin or its B subunit on the various subsets of lymphocytes has been confounded by their poor stimulatory and strong inhibitory properties on lymphocyte proliferation is not well understood (page 226, 2nd column). Nashar et al teach that the importance of receptor binding in the potent immunogenicity of EtxB was compared to an EtxB mutant (G33D) which lacks the ability to bind GM-1. Nashar et al teach that subcutaneous immunization of EtxB(G33D) resulted in 160-fold reduction in antibody titer as compared to that of wild-type EtxB and oral delivery of EtxB(G33D) failed to provoke any detectable secretory or serum anti-B responses. Nashar et al teach that the ability of toxoids to act as potential carrier for antigen is directly related to their ability to bind ganglioside receptors (page 230). It should be noted that Example 3 of the specification teaches that intranasal immunization with wild type EtxB serum induced a high antibody level and in contrast, EtxB(H57S) (an EtxB mutant) induced a significantly lower antibody response in comparison to wild type EtxB (page 43). Truitt et al, *(Infection and Immunity, April 1998, p. 1299-1308)* teach that novel agents that bind and modulate the function of immune cells are of interest for transplantation immunology, autoimmune disease, vaccine development and other related fields (page 1299, 1st column). Truitt et al teach that bacterial enterotoxins which bind to membrane glycosphingolipids (i.e. gangliosides) on lymphocytes may be useful as immunomodulatory agents to prevent or modulate T cell mediated disorders (page 1299, 1st column). Truitt et al teach that the relative level of GM-1 expression and availability for cross-linking may be important factors in the dose of recombinant EtxB required to suppress T cells, however the mechanism by which

recombinant EtxB induces apoptosis is not known (page 1307, 1st column). Truitt et al teach that previous studies have shown that CtxB is significant to prevent Graft-Versus-Host Disease (GVHD) following allogenic bone marrow transplantation in mice, however whether induction of apoptosis or immune deviation or both contribute to decreased GVHD is unclear at present (page 1307, column 2).

It has been recognized by the previously cited art that the mechanism by which the binding of enterotoxins to GM-1 receptors result in poor stimulatory and strong inhibitory properties on CD8+ T cells in regard to autoimmune disease is not well understood in the art and it is also recognized in the art and supported by the specification that EtxB mutants do not cause apoptosis of CD8+ T cells, however, EtxB mutants show reduced antibody titers after oral and subcutaneous administration. Clearly a great amount of experimentation would be necessary in order to develop a peptide wherein the peptide does not exhibit GM-1 binding activity to be used in a method of a subject having an autoimmune disease, human T cell leukemia, transplant rejection or graft-versus host disease. One skilled in the would require guidance in order to make and use the claimed invention in regard to preventing and treating autoimmune diseases with a peptide that does not exhibit GM-1 binding activity (i.e. a EtxB mutant). The claimed invention also broadly encompasses the treatment of any infectious disease caused by any microorganism or any allergy caused by an agent. The specification has not provided enablement for a peptide that treats any infectious disease or any allergy since the instant specification does not make a correlation between GM-1 binding activity, the lack of GM-1 binding activity, EtxB, CtxB, infectious

diseases or allergies. One skilled in the art would require guidance in order to make and use the claimed invention in regard to preventing and treating any infectious disease or any allergy.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification regarding a method of treating a subject having an autoimmune disease, human T cell leukemia, transplant rejection or graft-versus host disease, allergies or infectious disease comprising administering to the subject an effective amount of a peptide wherein the peptide does not exhibit GM-1 binding activity, 3) there are no working examples presented in the specification that teach the use of the claimed method, 4) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level), and 5) the state of the art in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, it is determined that it would require undue experimentation to make and use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 34 and 35 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 34 and 35 recite "exhibit activity the same or similar to EtxB or CtxB", it is unclear as to what the applicant is referring? What activity is attributed to EtxB or CtxB?

10. Claim 34 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because the abbreviations EtxB and CtxB are used. The proper name of the toxins should be "*Escherichia coli* heat labile entertoxin B" and "cholera toxin B", respectively used at the first occurrence of these terms in the claims or specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 34-35 are rejected under 35 U.S.C. 102(b) as anticipated by Williams et al, *(WO 97/02045, published January 23, 1997).*

Claims 34 and 35 are drawn to a method of treating a subject having an autoimmune disease, human T cell leukemia, transplant rejection or graft-verses host disease, allergies or infectious disease comprising administering to the subject an effective amount of a peptide selected from the group consisting of SEQ ID NO 2, 3, 4 and 5, mixtures thereof, homologues, variants, and derivatives of any of these, which exhibit activity the same or similar to EtxB or CtxB, but wherein the peptide does not exhibit GM-1 binding activity.

Williams et al disclose methods for the prevention or treatment of autoimmune disease (claims 3-4, page 44), transplant rejection or graft-versus –host disease (claims 12 and 14 pages 45-46) in which an effective amount of an agent (i.e. a peptide having an effective on GM-1 mediated intracellular signaling events but no GM-1 binding activity). Williams et al also disclose a method for the vaccination of a mammalian subject in which an effective amount of an agent (i.e. a peptide having an effective on GM-1 mediated intracellular signaling events but no GM-1 binding activity) is administered to a subject. Williams et al also disclose that the agents used in vaccinating a mammalian subject can be an agent having an effect on GM-1 binding mediated intracellular signaling events but no GM-1 binding activity (see the Abstract). The amino acid sequence that is the same or similar to SEQ ID NO:2 would be inherent in the teachings of the prior art.

Since the Office does not have the facilities for examining and comparing applicant's peptide with the peptide of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the peptide of the prior art does not possess the same material structural and functional characteristics of the claimed peptide). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Status of Claims

12. No claims are allowed.

Conclusion

13. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
January 20, 2003

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